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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : David F. Englert
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Title : DERIVATIVE NUCLEIC ACIDS AND USES THEREOF

Art Unit : 1655
Examiner : A. Chakrabarti

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Fields
2/14/02

Commissioner for Patents
Washington, D.C. 20231

AMENDMENT & RESPONSE TO ACTION DATED JULY 5, 2001

AMENDMENTS:

In the specification, replace the paragraph beginning at page 48, line 14 with the following rewritten paragraph:

a1

-- A derivative nucleic acid is a nucleic acid which includes a capture tag sequence at one or both of its termini in a single strand overhang. The derivative sequence is produced only upon the hybridization of a probe, which include the sequence tag as an internal fragment, to the target sequence for which it is specific. --

Replace the paragraph beginning at page 49, line 10 with the following rewritten paragraph:

a2

-- The capture tags used in methods of the invention are initially supplied as internal sequences, i.e., they are flanked on both sides with other sequences. Only after a target sequence specific reaction are tags found at the terminus of a nucleic acid. The internal positioning makes it very difficult for un-reacted tag-containing probes to hybridize to a capture probe. On the contrary, reacted molecules, which present the tag sequence at a terminus, hybridize readily with

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capture probes, particularly partially duplex probes having a single strand over hang which is complementary with a tag sequence. --

In the claims, cancel claims 7-35, as these claims belong to un-elected restriction groups.

Amend claim 1 as follows:

1. (first amended) A method of analyzing a plurality of target nucleic acid sequences in a sample, the method comprising:

providing, for each target nucleic acid sequence to be analyzed, at least one probe/primer molecule which probe/primer molecule includes a region of sequence substantially complementary to a sequence in the target nucleic acid sequence and a region that is not located at either terminus of the probe/primer and which includes a capture tag sequence;

forming a reaction mixture which includes the probe/primer molecules and the target sequences under conditions such that, if a probe/primer molecule specific for a target sequence and that target sequence are both present, one or a plurality of derivative molecules having a capture tag at one or both its 3' or 5' termini, of the probe specific for the target sequence, is generated; and

evaluating the presence of one or more derivative molecules, each derivative molecule indicating a target nucleic acid sequence in the sample, thereby analyzing the plurality of target nucleic acid sequences in the sample.

Claims 2 to 6 are reiterated as follows:

2. (reiterated) The method of claim 1, wherein the derivative nucleic acid molecules are analyzed by hybridizing the tag sequences to capture probes which are spatially separated.

3. (reiterated) The method of claim 2, wherein the capture probes are partially duplex probes with capture tag-complementary single stranded overhangs

4. (reiterated) The method of claim 2, wherein the capture tags are disposed on beads.

5. (reiterated) The method of claim 2, wherein the capture tags are disposed on an ordered array.

6. (reiterated) The method of claim 2, wherein the derivative nucleic acid is ligated to a capture probe and then washed.

Please add claim 36-41.

-- 36. (new) The method of claim 1, wherein the probe/primer molecule comprises a restriction endonuclease recognition site.

37. (new) The method of claim 36, wherein cleavage of the probe/primer molecule with the restriction endonuclease leaves the capture tag sequence in a single-stranded overhang.

A4

38. (new) The method of claim 36, wherein the restriction endonuclease recognition site is a Type IIS restriction endonuclease recognition site.

39. (new) The method of claim 1, wherein the forming comprises cleaving probe/primer molecules that are annealed to target sequences with a restriction endonuclease.

40. (new) The method of claim 39, wherein the restriction endonuclease is a Type IIS restriction endonuclease.

41. (new) The method of claim 1, wherein the forming comprises cleaving probe/primer molecules with a flap endonuclease. --

REMARKS:

In the action mailed July 5, 2001, claims 1 to 6 have been rejected. Applicant has amended claim 1 and added new claims 36-41. No new matter has been added.

Examiner's comments are reiterated below in bold, block-face type.

3. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 1, the preamble of the instantly claimed method is drawn to a method for multiplexed analysis of a plurality of target nucleic acid while the final process step is that of evaluating the presence of one or more capture sequence tags and it is thus unclear as to whether the instantly claimed methods are drawn to a method for multiplexed analysis of a plurality of target nucleic acid or rather evaluating the presence of one or more capture sequence tags. Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 1 lacks such a last step and are confusing because the additional method step is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashions. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. Applicant. Int. 1986). It is suggested that an amended claim more clearly describing the intended steps be submitted.

The rejection is met by amendment of Claim 1. The method is a general method for analyzing a sample that includes nucleic acids. The amended claim includes a process that relates back to the preamble. The method includes analyzing the one or more derivative molecules to thereby analyze the sample.

5. Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Wong (U.S. Patent 5,935,793) (August 10, 1999).

Wong teaches a method for multiplexed analysis of a plurality of target nucleic acid sequences in sample (Abstract) comprising the methods of:

providing, for each target nucleic acid sequence to be analyzed, at least one probe/primer molecule which probe/primer molecule includes a region of sequence substantially complementary to a sequence in the target nucleic acid sequence and a region that is not located at either terminus of the probe/primer and which includes a capture tag sequence (Abstract and Figures 1A and 1B and Column 5, line 49 to column 6, line 7 and Tables 1-3);

forming a reaction mixture which includes the probe/primer molecules and the target sequences under conditions such that, if a probe/primer molecule specific for a target sequence and the target sequences are both present, one or a plurality of derivative molecules having a capture tag at one or both its 3' or 5' termini, of the probe specific for the target sequence, is generated, thereby producing a derivative nucleic acid suitable for evaluation (Figure 4 and Examples 1 and 2);

evaluating the presence of one or more capture sequence tags (Figure 5 and Column 20, lines 47-60).

The rejection is respectfully traversed. Wong teaches primer sequences that include a tag. For example, Fig. 1A of Wong depicts a "tag-primer" that has the tag positioned at the 5' terminus. This "tag-primer" is not generated from a molecule which has an internal tag. Fig. 1B of Wong depicts a "primer-tag-primer" in which the tag is internal. Wong discloses separate embodiments in which the "tag-primer" or the "primer-tag-primer" is used. Wong does not teach a derivative nucleic acid molecule that is formed by modifying, e.g., cleaving, a primer-tag-primer, in which the tag is internal, to reposition the tag at a terminus of the derivative molecule.

In contrast, the claimed method requires providing a molecule that initially includes an internal tag and forming a mixture that includes a derivative molecule in which the tag is repositioned to a terminus. Wong does not disclose or suggest such a modification of Wong's "primer-tag-primers," which the Examiner has compared to the (unrelated) probe/primer molecules of the claim. Thus, Wong does not anticipate the claimed invention.

7. Claims 1-6 are rejected under 35 U.S.C. 103 (a) over Wong (U.S. Patent 5,935,793) (August 10, 1999) in view of Zhang et al. (U.S. Patent 5,942,391) (August 24, 1991).

Wong teaches the methods of claims 1-5 as described above.

Wong does not teach the method wherein the derivative nucleic acid is ligated to a capture probe and then washed.

Zhang et al. teach the method wherein the derivative nucleic acid is washed and then ligated to a capture probe. (Column 40, lines 1-27 and Figure 5). However, MPEP 2144.04 further states, "*In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) Selection of any order of mixing ingredients is *prima facie* obvious".

The rejection under 35 U.S.C. 103(a) is respectfully traversed. The Examiner relies on Zhang *et al.* to cure deficiencies in Wong with respect to claim 6. Neither Zhang, Wong, nor the combination of Zhang and Wong suggests the method of claim 1 or claims depending from claim 1, including claim 6.

As seen above, Wong discloses "tag-primers" and "primer-tag-primers," but Wong does not teach or suggest a derivative nucleic acid molecule that is formed by modifying, e.g., cleaving, a primer-tag-primer, in which the tag is internal, to reposition the tag at a terminus of the derivative molecule.

Zhang teaches the ligation of target-specific probes. For example, Fig. 5 illustrates the annealing of two amplification probes to a target to form a complex, capturing of the complex

using a capture probe, ligation of the two amplification probes, and amplification of the ligated amplification probes. Zhang does not teach forming a derivative nucleic acid in which a capture tag sequence is reposition from an internal position to a terminal position.

Moreover, as neither Wong nor Zhang discloses or suggests the formation of the derivative nucleic acid required by applicant's claimed method, neither reference alone nor the combination makes the claimed method obvious.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a $920 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 7 Jan 02

Louis Myers
Reg. No. 35,965

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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